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EDITORIAL

On these pages the editor offers his opinions, unshackled by advertising patrons and unrestrained by anything save a sense of the decent and the truthful. The editor, alone, is responsible for their type, their tone and their tenor.

THE PHARMACOPOEIAL CONVENTION IS OVER

"The tumult and the shouting dies,
The captains and the kings depart,
Still stands thine ancient sacrifice
An humble and a contrite heart."

I SCARCELY know whether the foregoing lines aptly apply to the last Pharmacopœial Convention or not. But there was, before, and during the decennial meeting, the usual fanfare and foolishness; and at last the *strutting* kings and the *working* captains have returned to their belonging provinces. Long before the call that had brought the cohorts of delegates to Washington, the "old timer" had been given a prominent place in the alleged "mouthpiece" of the American Association of Colleges of Pharmacy, the *Journal of Pharmaceutical Education,* to rant and rave, over pharmacopœial policies, principles and personnel during the preceding decade.

And the editor of that Journal in his own characteristic way had aided and abetted the "old timer" in an effort to prove that everything about the management of the last revision had been wrong—particularly from a dietary standpoint.

It was even charged, in an absurd and absolutely false statement, that the Philadelphia College of Pharmacy and Science had dispensed honorary degrees to men connected with the Pharmacopœia, obviously to incur favor. This charge, incidentally, is now in process of legal survey, and properly so.

Over the country, these men spread reprints of their articles.

What authority was there for sending these reprints in envelopes bearing the label and presumably having the approval of a State supported university?

What warrant had men who never had contributed a mental molecule to pharmacopœial progress to sling mud at those who had made their *real* contributions to the cause?

The one satisfaction after all was that the "Blitzkrieg" of these men and their minions did not work. Certainly they succeeded in electing a revision committee largely of their own choice, and generally speaking a fortunate choice. Yet why were certain chemical experts whose long proven service had indicated their value eliminated from *their* revision committee? But the dénouement came when their candidate for the Chairmanship of the Revision Committee was absolutely ignored by the medical representatives and at the last minute wisely abandoned by some of his own alleged confreres.

Professor E. Fullerton Cook, whose work as Chairman for the past decade had been a splendid service yielding a splendid achievement was re-elected chairman for the forthcoming decade. This was, under the circumstances, a double tribute.

His address to the Convention was dignified and masterly and his new plans for a permanent pharmacopœial center were wise and well accepted. Chairman Cook's continuance in the work is insurance that the revision will be conducted efficiently and on schedule.

It is hoped that he will find in the new revision committee as useful and dependable a group as he found in the last, and that he will not hesitate to exercise his new prerogative to eliminate from the committee those unwilling to or incapable of cooperating effectively.

Pharmacy may be justly proud of the fine contributions it has made to the Pharmacopœia in the past. May it so continue in service and may those who feel the need *now,* for

"The humble and contrite heart"

find peace in penitence, and penitence in peace.

IVOR GRIFFITH.

REPORT TO THE UNITED STATES PHARMACOPOEIAL CONVENTION OF 1940 BY THE PHARMACOPOEIAL REVISION COMMITTEE OF THE PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE

THE formulation of decennial reports by Pharmacopœial Committees of the Philadelphia College of Pharmacy and Science has been accepted by this college as one of its duties and privileges for more than a hundred years. In the preface to the Pharmacopœia of 1830, the assistance of the committee of this college is especially mentioned. In 1840 a similar committee voluntarily undertook the revision of the entire Pharmacopœia, and the records show that about one hundred and twenty-five meetings were held within that year, and the complete manuscript of a revised Pharmacopœia was submitted to the medical members of the Revision Committee. This revised Pharmacopœia is recorded in the preface as forming the basis for the U. S. P. of that decade (1840).

The names of those who have carried forward this national service are the names of men in American pharmacy who have actively participated in every pharmaceutical development in this country—Daniel B. Smith, the first editor of a journal of pharmacy in America, and the first president of the A. Ph. A.; William Proctor, Jr., universally honored as the "Father of American Pharmacy"; Edward Parrish, the first author of a pharmaceutical text in this country; J. M. Maisch, pioneer in the standardization of vegetable drugs; Joseph P. Remington; Martin I. Wilbert; George M. Beringer; Henry Kraemer; Charles H. LaWall, and many others who built the foundations on which this established tradition rests.

When Dr. Wilmer Krusen, President, invited co-operation this year, over sixty members of the college organization, and others who were interested, voluntarily offered their services. The main committee was divided into nine sub-committees, and these sub-committees have held many conferences and some members from a distance have also offered valuable suggestions for the report.

It is only fair to record the fact that in continuing this intensive interest in the publication and perfection of the Pharmacopœia, the members have been inspired by the spirit of nation-wide service which has always been a policy of the institution. Throughout the years

this has been taught as one of the duties of the college. One of the animating influences back of its organization in 1821 was the recognized need for perfection of drug standards.

The reports herewith submitted represent this spirit of unselfish service and are offered with the hope that they will assist in the perfection of the Twelfth Revision of the United States Pharmacopœia. The several sub-committees making reports with their chairmen and members are listed below:

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George W. Patterson — Gerald F. Rorer
Allen F. Peters — George A. Tushim
Paul S. Pittenger — Charles E. Vanderkleed
Paul W. Wilcox

and, in addition,

Donald P. LeGalley, with a paper entitled "Efficiency of Various Desiccants in Preventing Moisture Absorption by Packaged Vegetable Drugs and Chemicals."

FINAL REPORT OF THE P. C. P. & S. SUB-COMMITTEE ON SCOPE

I. We recommend:

That the substances used only for diagnostic purposes (such as Phenolsulphonthalein and Fluorescein) should be omitted from the body of the Pharmacopœia and described either among the Reagents or in a separate division of the Pharmacopœia. They are not drugs within the meaning of the Pure Food and Drugs Act as they are not used in the "cure, mitigation or prevention of disease."

II. We recommend:

That the following drugs, recognized in the U. S. P. XI, be omitted from the U. S. P. XII for the reason that the infrequency with which they are prescribed indicates that the medical profession does not regard them as therapeutically important:

Acidum Acetyltannicum
Acidum Oleicum
Acidum Stearicum
Alumen Exsiccatum
Arsenii Triiodidum
Cannabis
Extractum Glycyrrhiza
Extractum Malti
Glyceritum Amyli
Hydrargyri Succinimidum
Liquor Arseni et Hydrargyri Iodidi
Liquor Hepatis (for oral use)
Myrrha
Oleum Maydis
Potassii Citras Effervescens
Spiritus Lavandulae

III. The following we believe have sufficiently established themselves to merit admission to the U. S. P. XII:

A. Aluminum Hydroxide
Amphetamine (Benzedrine)
Dilaudid (Dihydromorphinone Hydrochloride)
Ergonovine

Glycocoll (Aminoacetic Acid)
Insulin
Insulin Zinc Protamine
Magnesium Trisilicate
Metrazol (Pentamethylenetetrazol)
Oleum Hippoglossi (Halibut Liver Oil)
Sulfapyridine
Syrup Ammonium Mandelate
Triethanolamine
Urea

B. Concerning the following, the sub-committee is undecided, but feel they deserve serious consideration for admission:

Allantoin
Aluminum Silicate Gel
Calcium Mandelate
Nikethamide (Coramine)
Desoxycorticosterone Acetate
Dehydrocholic Acid (or similar biliary derivative)
Estradiol
Estrone
Progesterone
Sobisminol Mass
Testosterone
Gas gangrene Antitoxin
Tetanus Toxoid

Respectfully submitted,

H. C. Wood, Jr., *Chairman,*
Sub-Committee on Scope.

SUGGESTIONS FOR REVISION OF THE PROXIMATE ASSAY METHODS OF THE U. S. P. XI

A critical study of the chapter on Proximate Assays and the assays for specific substances show that the general directions and assays of the U. S. P. XI are generally satisfactory, particularly so since the appearance of the two supplements. A highly desirable need

is uniformity of directions and consistent phraseology. This procedure would simplify directions and eliminate many words, and in some instances the larger part of sentences. A striking illustration of this point is seen under the following sentence in assay of Ipecac: "Decant into a separator 50 cc. representing 5 gm. of Ipecac, accurately measured, of the clear supernatant liquid, rinsing the measuring vessel with a small quantity of ether and adding the rinsings to the solution in the separator." The following phrasing is suggested: "Accurately measure 50 cc. of the clear liquid and place in separator. Rinse the measuring vessel with ether, adding the rinsings to contents of separator." On the second line of this assay it is directed to use "ether, which is free from peroxide." Directions to use peroxide-free ether is sufficient. This phrasing is used later in the assay. Another instance of this type of phrasing is used under the assay of Codeine Phosphate in the first supplement which directs as follows: "Dissolve about 0.5 gm. of Codeine Phosphate, accurately weighed, in 10 cc. of distilled water, in a separator" etc. We suggest the following wording: Accurately weigh about 0.5 gm. of Codeine Phosphate, place in separator and dissolve in 10 cc. of distilled water. There is no saving of words here, but the phrasing is much less involved and clearer. These and many other instances show that careful editing is required, thereby promoting clarity, brevity, uniformity of phrasing, and conserving valuable space in the Pharmacopœia.

Citrated Caffeine

On the second line of assay, add the words, place in separator, after the words, constant weight at 80 degrees C.

Ephedrine

The second supplement of the U. S. P. requires the use of five drops of methyl red T. S. in the titration of the alkaloid. This amount is excessive and should be left to the discretion of the operator as in the assay of Ephedrine Sulfate. Directions should be given to use methyl red T. S. to neutralize the alcohol used to dissolve the alkaloidal residue before titration. If one drop of the indicator was used for this purpose, no more need be added.

Fldext. Ginger

The assay method should be more adequately controlled, particularly during the evaporation of the alcohol. A loss of the active principle occurs at this point.

Nux Vomica

It is recommended that total alkaloids be determined as in the U. S. P. IX and U. S. P. X. The present assay for strychnine content is uncertain, particularly the section devoted to the oxidation of the brucine.

The second paragraph of the assay in supplement one contains directions for a repetition of the just completed acid and chloroform "shake outs." The reason for this is not apparent and is newly added as the underscored portion of the paragraph.

Compound Tincture of Cinchona

Twenty-five cc. instead of the required 50 cc. is ample for assay. The presence of 7.5 per cent. of glycerin in the tincture requires a change in line 4 of the assay by adding the word "nearly," so that the phrase reads, "continue the evaporation *nearly* to dryness."

The assay of Compound Tincture of Cinchona should be studied with the intent of shortening the method by using less tincture and eliminating the need for evaporation and treatment on asbestos or paper pulp.

Tincture of Nux Vomica

The recommendation and observation noted for Nux Vomica also apply to the tincture. In addition, it is considered that the use of 100 cc. of tincture for assay is excessive. Twenty-five cc. representing approximately .030 gm. of strychnine is sufficient. The use of this amount would make it unnecessary to concentrate the tincture before assay.

Opium

It is recommended that the solution of the morphine using methanol be eliminated from the assay. It is felt that the methanol is not necessary and that nothing is gained by its use.

Constant Weight

A clarification of this term as given on page 3 of the U. S. P. under General Directions is needed. The definition now states "that two consecutive weighings do not differ by more than 0.1 per cent." There is a difference of opinion as to whether it refers to 0.1 per cent. of the residue obtained or to 0.1 per cent. of the material under examination.

Alkaloids and Alkaloidal Salts

It is recommended that assay methods be given for Atropine, Atropine Sulfate, Codeine, Codeine Sulfate, Morphine Sulfate, Quinine Sulfate and the other alkaloids and alkaloidal salts of the U. S. P. Assays are now given for Citrated Caffeine, Codeine Phosphate, Ephedrine, Ephedrine Hydrochloride, Quinine and Urea Hydrochloride and others. These assays would fulfill a need and provide pharmacopœial consistency.

Moisture

It is recommended that where a moisture determination is part of the rubric of a substance, the method (toluene method or some other) to be used be specifically stated and also, the temperature at which the determination is to be made.

Respectfully submitted,

JOHN ROBERTS, *Chairman,*
C. C. PINES, *Secretary,*
Proximate Assays Committee.

REPORT OF THE SUB-COMMITTEE ON NOMENCLATURE

The Sub-Committee on Nomenclature is cognizant of the fact that the devising of a pharmacopœial title may involve problems in science, in industrial production, or in law enforcement, as well as problems in language. The committee, as a consequence, is not inclined to be hypercritical of the titles now official, and is inclined, rather to be conservative in its recommendations. The following are submitted:

1. That Latin and English titles official in the U. S. P. XI, and presumably well established by usage, be not radically changed except for compelling reasons.
2. That this be not interpreted as opposition to the deletion of unnecessary adjectives, or to other minor alterations which may be deemed desirable.

3. That the employment of the adjective "compound" be continued in titles of preparations or mixtures, if the alternative is the inclusion in the title of the names of more than two ingredients.

4. That *new* Latin and English titles be as concise as possible—brief enough to admit of their general employment by physicians in prescription writing.

5. That in Latinizing the English names of new medicinal substances to be admitted to the Pharmacopœia, the appending of third declension endings be avoided whenever possible, for it is important not only that the Latin title be as short as possible, but also that its genitive may be derived without difficulty. This is not always the case with third declension words.

6. That in the case of third declension words now official, the abbreviated title be given also in the genitive whenever the abbreviation of the nominative is not correct for the genitive.

   Examples: Nom.—Magma. Mag.
   Gen.—Magmat. Mag.
   Nom.—Carbo Activat.
   Gen.—Carbon. Activat.

7. That in the case of some of the newer titles, which have not as yet become firmly established by usage, and which are too involved and too difficult as to spelling to admit of their general employment in prescription writing, radical replacements by simpler titles might well be considered.

   As a case in point:

   Toxinum Diphthericum Detoxicatum might be replaced by the Latinized English title, namely, by Toxoidum Diphthericum. There is justification for the use of short titles—even coined names—for such difficult and involved names as Erythritylis Tetranitras Dilutus, Theophyllina cum Aethylenediamina;—and we hope that such replacements may be possible.

8. That the use of such titles as Chloramina-T, Dichloramina-T, be discontinued. Since the toluene compounds are the only chloramines official, the T could be deleted without danger of ambiguity.

9. That we recommend the use of correct chemical names as titles for the vitamins (so-called) as far as this is possible. Such titles as Acidum Ascorbicum for vitamin C, and Thiaminae Hydrochloricum for vitamin B_1, now in the Second Supplement, are most acceptable.

   The word vitamin itself is, from the standpoint of chemistry, a misnomer, and should be continued only as a synonym. Such titles as Vitaminae A et D Naturales in Oleo are not only too involved, but are also (as far as the Latin is concerned) a most undesirable innovation in pharmaceutical nomenclature.

10. That we recommend the inclusion in the chapter entitled General Notices a paragraph on the use of the word compound (Latin, compositus, -a, -um) in official titles. Further, that the following phrasing be submitted to the Revision Committee for their consideration:

The occurrence of the word "Compound" (Latin Compositus -a, -um, abbreviation Co.) in titles of preparations in this Pharmacopœia, in the interest of accuracy, brevity and safety, and in conformity with long usage, shall be understood to indicate that there is present in the preparation one or more physiologically active ingredients other than that or those specifically mentioned in the title of said preparation.

Respectfully submitted,

J. W. STURMER, *Chairman*
RALPH CALVERT, *Secretary.*

FINAL REPORT ON SUGGESTED CHANGES FOR THE BOTANY AND PHARMACOGNOSY OF THE U. S. P. XII BY THE SUB-COMMITTEE ON BOTANY AND PHARMACOGNOSY OF THE PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE

The first meeting of the sub-committee was held on December 4, 1939. It was then decided to hold regular meetings on Monday mornings of each week, to cover the botanical monographs in sequence,

and offer suggestions during the meeting. The members present at these meetings were Dr. Dunn, Professors Stoneback and MacLaughlin, and Mr. Brillhart. Correspondence was maintained with the absent members of the sub-committee.

By virtue of its conferences and correspondence, the sub-committee recommends to the Chairman of Sub-Committee No. 5, Botany and Pharmacognosy of the Committee of Revision of the U. S. P. XII the consideration of the following changes:

I. A review of all the monographs by competent workers in order that the descriptive language may be placed on a more consistent and scientific basis, with some elaboration in places. Specifically noted are:

ASPIDIUM—Include the region of the pericycle in the description.

CANTHARIS—Rewrite description in correct entomological terminology.

CAPSICUM—Rewording to include Epicarp cells and "Giant" cells.

CARUM—Rewrite, using consistent terminology.

CARYOPHYLLUS—Rewrite to include such terms as Hypanthium, imbricated membranous petals, Schizolysigenous reservoirs. Pollen grains *occasional* according to many observers.

CASCARA—More elaborate and accurate description, mention collenchyma cells in powder.

CHRYSAROBIN—Should test; green fluorescence with alkali hydroxide be included?

COCCUS—Rewrite using correct entomological terminology.

DIGITALIS—Elaborate upon description and include veins of fourth order; further investigation of moisture and packaging requirement.

ERGOT—Rewrite using correct mycological terminology, further investigation of moisture and packaging requirement.

ERIODICTYON—Correct description of lower epidermis.

GALLA—Mention parenchyma and lignin bodies.

GENTIAN—Include description of both rhizome and root.

IPECAC—Mention phloem and cambium regions, starch simple and two to eight compound.

LINUM—Use term "spermoderm," include size and description of aleurone.

MEL—Should description of pollens from undesirable sources as Kalmia be included?

MENTHA PIPERITA AND MENTHA VIRIDIS—Rewrite on more scientific basis to include terms as "Verticillaster," etc.

MYRISTICA—Mention "raphe" and "ruminate albumen."

NUX VOMICA—Seed coat or spermoderm is external, not internal.

OPIUM—Mention rumex leaves and granular fragments of *latex*.

PODOPHYLLUM—What is meant by "internally showing a corky epidermis"?

PRUNUS VIRGINIANA—Mention cork cambium.

SARSAPARILLA—Correct description of hypodermal and endodermal cells in Mexican sarsaparilla.

SENNA—Should the distance between epidermal hairs on the two varieties be used as a means to differentiate.

SINAPIS NIGRA—Appearance of epidermal cells under polarized light.

TRAGACANTH—Under "structure" note that drug must be soaked in water so as to see lamellae.

VALERIAN—Much valerian is now young, small and *uncut*.

VERATRUM VIRIDE—Some received as longitudinal *slices*.

PITUITARIUM POSTERIUM—Include microscopical description.

II. The general notices should include a statement as to the true meaning of macroscopical measurements. We have investigated many commercial samples of usable drug, labelled U. S. P., which are at great variance with the requirements. Especially noted are: Aspidium, Ipecac, Podophyllum, Rhubarb, Valerian, Glycyrrhiza, Senna. Others will be recorded in a paper now being written.

III. The general notices should include a statement as to the true meaning of microscopical measurements. Suggested is the statement of an average measurement with the maximum and minimum in parentheses directly following: Should all microscopic measurements be stated in microns? Should the term "micron" or μ be used for small measurements if measurements are to be stated in microns?

IV. Mention of the ultraviolet effect when it is a characteristic of a crude drug. (Example, Hydrastis.)

V. We suggest that the U. S. P. consider adoption of color standards for powdered crude drugs and for whole crude drugs wherever possible.

VI. Readmission of Dryopteris marginalis as a source of aspidium, with a proper descriptive monograph.

VII. Correction: Cardamon; dimensions of calcium oxalate crystals should read 0.010 to 0.025 mm. instead of cm.

VIII. Are assays required for sarsaparilla (saponin), senna and aloes (cathartic value) and capsicum (to replace organoleptic test)? We suggest a check of those assays offered and further investigations.

IX. Whenever tests are mentioned in the monographs it would be advisable to mention the name of the substance present or absent as indicated by the test. Mesquite gum in Acacia, Vanillin in Asafoetida, Hesperidin in Bitter Orange, Bdellium as differentiated from Myrrh, etc.

SUGGESTIONS FOR REVISION OF THE SURGICAL AND BIOLOGICAL PRODUCTS IN THE U. S. P. XI

Biological Products

1. *All serums, antitoxins and all preparations which are either the serum or obtained from the serum of the blood of animals.*

There is no reason why mention should be made specifically in the definition (see U. S. P. XI, pages 58, 59, 60, 331, 332, etc.) that

the product "is obtained from the blood of an animal of the genus *Equus.*" The procedure as used in the British Pharmacopœia (see pages 59, 60, 385, etc.) is more satisfactory. The statement is made here that it is prepared "from the blood of animals" which is to meet all the mentioned requirements.

If the U. S. P. sees fit to adopt the above procedure, the following statement not present in the U. S. P. should be included in all instances: "Labels and circulars attached to the marketable product should indicate the genus of the animal employed."

The above is suggested so as to avoid the necessity of having to make changes in succeeding supplements, as was done in the case of Antitoxinum Tetanicum (see U. S. P. XI, page 60, and U. S. P. Second Supplement, page 20). In fact, in the latter instance (see Supplement), the above suggestions are used. It should be carried out along the same line with all other serums and serum products.

2. *Assay*

The U. S. P. XI speaks of units under Cod Liver Oil (page 261), but defines such unit (see pages 478-484 incl.). The U. S. P. gives extensive assay methods for vitamins, anti-anemia products, etc. (page 478). Yet not a word is said about the assay of serums, antitoxins and similar biological products other than the fact that the unit (see page 59) "shall be that of the standard diphtheria antitoxin distributed by the National Institute of Health of the U. S. Public Health Service." On page 332, mention is not made as to what the potency is, other than the fact that the expiration date is to state when the potency has been lost. Under Diphtheria Toxoid (on page 408) an explanation is given as to the requirements for the toxicity and the antigenic value of this product. Why? The statement that "the potency should be as prescribed by the National Institute of Health of the U. S. Public Health Service" would have been sufficient here as we are led to believe it is sufficient under the antitoxins. One might also observe a definition for the M. L. D. of Diphtheria Toxin (on page 409) and for the skin test dose of Scarlet Fever Streptococcus Toxin (on page 410). In the Second Supplement (pages 97 and 98), the dose of Antipneumococcus Serum is given in units. Nothing is said as to what a unit is or even that the unit must conform to that distributed by the National Institute of Health. The latter error of course must be corrected.

The Ministry of Health, with the co-operation of the Medical Research Council, serves in Great Britain in a capacity similar to the National Institute of Health in our country. The B. P. must use the standards of the former, but it includes them in all instances either in the write-up or in the appendix.

We recommend that the U. S. P. include statements as to what is meant by the term units used in several instances and give assay methods and standards for all official biological products (methods of determining potency) wherever such are available as is now done with vitamins, anti-anemia preparations, numerous galenicals and active drugs, catgut, etc.

3. *Nomenclature*

a. Antitoxinum Scarlatinae Streptococcicum (U. S. P. XI, page 59). If this title is to be used, then the English title should be "Scarlet Fever Streptococcus Antitoxin" in accordance with a similar translation of the toxin (page 410).

b. Toxinum Scarlatinae Streptococcicum. It would lend itself to better usage to drop the Streptococcicum in both (a) and (b). Let it be Scarlet Fever Antitoxinum and Scarlet Fever Toxin.

c. Serum Antipneumococcicum (Second Supplement, U. S. P., page 97). The English and Latin titles are misleading. The definition in the U. S. P. refers to type specific serums, made separately from one of five specific types. The term type specific should therefore be included in the English and a corresponding term in the Latin titles. As it now stands, a manufacturer cannot use the U. S. P. title, Serum Antipneumococcicum, for a type iv or a type xiv serum as these latter specific types are not official.

d. Toxinum Diphthericum Detoxicatum (page 408, U. S. P. XI) should be changed to Toxoidum Diphthericum. The present Latin title is not satisfactory.

e. Toxinum Diphthericum Diagnosticum (page 409). The English title should be Diphtheria Toxin for Diagnostic Use. The present English title is not a translation of the Latin title as it should be. The present English title should be carried as a synonym.

4. *Vaccinum Typhosum, etc.*

Under Vaccinum Typhosum and Vaccinum Typho-Paratyphosum, the following should follow the word "of" (second word in sec-

ond line of definition): "suitable antigenic strains of." Unless suitable strains that are antigenic are used, the vaccines will be valueless for the purposes intended. If the assay or potency suggestion recommended before will be included, this will take care of the above recommendation.

5. *Vaccinum Variolae*

Under Storage, following the word "in" and before the word "hermetically sealed," add the word "individual."

6. *Dosage, and Other Comments*

Under Diphtheria Toxoid the average dose is given as 1 cc. Under Vaccinum Typhosum the average dose as given comprises three injections. It is a known fact that the average dose of Diphtheria Toxoid is repeated until a negative Shick test is obtained. If the three injections are to be included under Typhoid Vaccine, a more detailed statement of the average dose is to be included under Diphtheria Toxoid, and if for no other reason than for the sake of uniformity the following or a similar statement is to be included, "to be repeated at proper intervals until the individual will give a negative Shick test." Note a similar statement under Scarlet Fever Streptococcus Toxin that graduated doses are given until a negative Dick test is obtained.

Under Scarlet Fever Streptococcus Toxin we find the statement under dosage: "for active immunization." Under Diphtheria Toxoid, Typhoid Vaccine and other places where active immunization is employed the average dose is mentioned as "prophylactic." Again for uniformity either one of the two phrases should be employed throughout, rather than speak of prophylactic dose in one place and the active immunization dose in another. The answer may be given that under Scarlet Fever Antitoxin there is included a prophylactic dose and inasmuch as the latter preparation is used in passive immunity, the term, "active immunization," is more desirable when considering dosage under "scarlet fever streptococcus toxin." But the same conditions prevail in the case of diphtheria antitoxin and diphtheria toxoid and in both instances, the phraseology employed is the term "prophylactic." The term "for active immunization" is to be preferred for all antigens as the vaccines, toxins, toxoids, etc. The term "prophylactic" is to be preferred for preparations containing

antibodies, as the antitoxins and serums, where prophylactic doses are employed.

In the description on page 409, "Diphtheria Toxin for the Shick Test is a solution," the word "sterile" should precede the word "solution" as in definitions given for other soluble products of bacterial growth on pages 408, 410 and 415. It is of course true that in small type the statement is given, "The product must be sterile," but including the word "sterile" in the sentence where the larger type phrase describes the preparation is desirable.

The average dose under "Rabies Vaccine" should have the statement—"Active immunization, by hypodermic injection" preceding the present phraseology just as is mentioned under typhoid vaccine and under the other biological products. Under "Smallpox Vaccine" nothing is said about the dose. Why this is not given is not clear, as all of the other biological products have the average dose mentioned.

7. Additions

We recommend that the following biological products be included:

Gas Gangrene Antitoxins
Whooping Cough Vaccine
Purified Protein Derivative (Tuberculin)
Alum Precipitated Tetanus Toxoid

The Efficiency of Antiseptics

The designation of substances as antiseptics implies that they possess certain characteristic properties; and specifically, the latter are the rendering of microorganisms innocuous either by actually killing them or preventing their growth, according to the character of the preparation or the method of application. There are many substances official in the U. S. P. which are employed as antiseptics or bacteriostatic agents. In most instances chemical analyses are possible, and a direct relationship exists between the chemical findings and the antiseptic or bacteriostatic value for each individual substance. In some instances, however, chemical analyses are either not possible or there exists little or no relationship between the chemical findings and the antiseptic or bacteriostatic property. In other cases we find that even in those substances where a relationship exists when each substance is tested and subsequently used by itself, the efficiency

may vary markedly from the proportionate chemical content when the substance is compounded with other ingredients or added to various vehicles, either liquid or ointment. Bacteriological methods to determine the efficiency of such preparations are possible both as a means of evaluation and especially as a means of standardization.

Testing disinfectants *in vitro* by the present methods may not always yield findings which will give an accurate indication of their activity in practice. But *in vitro* testing does offer a means of standardizing substances and preparations of them, so that they are always uniform. The National Formulary Committee on Antiseptic Testing is making valuable contributions along these lines.

We recommend that the U. S. P. Revision Committee consider bacteriological methods for the standardization of all substances and preparations where other methods are not available for such evaluation.

Ointment Vehicles

Various therapeutic substances and especially antiseptics have proved to be more effective when used in the newer water-miscible ointment bases not only in *in vitro* but also in *in vivo* experiments. We recommend that the U. S. P. Revision Committee arrange for a thorough study of these water-miscible ointment bases as they appear to be more satisfactory vehicles for bactericidal agents than other ointment bases.

Surgical Products

Silk sutures are widely used today. The question of "sizes" has been one which has been the concern of many surgeons. There is frequently no relationship and certainly no uniformity between silk sutures labeled with the same sizes by two or more different manufacturers. Furthermore, there is no relationship between the sizes of silk sutures and the corresponding sizes of catgut sutures. There appears to be little agreement among manufacturers of silk sutures as to other problems affecting the latter which are the concern of the surgeon. We recommend that the U. S. P. Revision Committee follow through along the lines as practiced for catgut sutures, and arrange for uniform and standardized sizes of silk sutures.

We also recommend the inclusion and standardization of the following surgical dressings: sterile surgical gauze; sterile adhesive plaster; and plaster-of-paris bandages.

On page 127 of the Second Supplement to the U. S. P. XI, under Sterility Tests, instead of the statement "Take portions of the substance in triplicate," when referring to cotton, gauze and related substances, we recommend that an approximate amount either in weight or preferably in square centimeters be designated.

Respectfully submitted,

LOUIS GERSHENFELD, *Chairman,*
Sub-Committee on Surgical and Biological Products.

SUGGESTIONS FOR REVISION OF CHEMICAL AND PHYSICAL STANDARDS AND TESTS IN THE U. S. P. XI

By the Sub-Committee on Chemistry and Physics of the Committee on Pharmacopœial Revision of the Philadelphia College of Pharmacy and Science

The following recommendations and suggestions, based upon the experience and personal observations of members of this sub-committee, are respectfully submitted for consideration by the Committee on Revision of the United States Pharmacopœia.

Specific Monographs

Acetanilid—An assay or test for purity, based on bromination of aniline obtained by hydrolysis, is considered advisable.

Acidum Acetylsalicylicum—Phenol red is preferred by many analysts for the titration of salicylic acid. The British Pharmacopœia Commission's General Chemistry Committee recommends use of this indicator in the assay for acetylsalicylic acid.

Acidum Benzoicum—Phenol red is, both theoretically and practically, a better indicator in the assay than phenolphthalein (see the paper by Kilpatrick and Chase, J. A. C. S., *53*, 1734, 1931, on the determination of solubility of benzoic acid, for example). Further, there is no really valid reason for persisting in the use of barium hydroxide in this and a few other (but not all) assays of this type. Sodium hydroxide is readily prepared carbonate-free and maintained in this state.

Acidum Mandelicum—Extension of the upper limit for melting point by one degree, to 121 degrees C., is recommended.

Acidum Phosphoricum—Thymolphthalein is a better indicator than phenolphthalein in the assay; with phenolphthalein the end-point appears too soon. (See Kolthoff and Sandell's "Textbook of Quantitative Inorganic Analysis," 1936, page 439, for a proof of this statement.)

Acidum Phosphoricum Dilutum—See preceding comment.

Acidum Salicylicum—Same recommendations as for benzoic acid.

Acidum Trichloraceticum—The final paragraph under "Assay" appears to be unnecessary.

Agar—Attention is called to the fact that this article, as brought into the market in bales, mostly from Japan, contains more water than 18 per cent., frequently containing as much as 22 per cent. A higher limit of moisture content might be considered.

Alumen—Use of phenol red in the assay in order to avoid excessive alkalinity is recommended. See discussion of this point in Kolthoff and Sandell's "Textbook of Quantitative Inorganic Analysis."

Ammonii Benzoas—Sodium hydroxide volumetric solution and phenol red indicator are recommended for use in the assay. See the recommendation for benzoic acid.

Ammonii Bromidum—Is the statement "Each gm. of Ammonium Bromide, previously dried, is equivalent to not less than 101.1 cc. and not more than 103.0 cc. of tenth-normal silver nitrate" necessary?

Ammonii Chloridum—Preference for the use of an adsorption indicator in the assay is expressed by a member of the sub-committee. Another member finds the end-point indefinite but recommends tetrahydroxyquinone (THQ—Betz Laboratories, Philadelphia) as an indicator which yields excellent results in checking assays for inorganic halides by direct titration.

Ammonii Salicylas—Same comment as for ammonium benzoate.

Aqua Destillata—The test with methyl red and with bromthymol blue solution is reported to be unsatisfactory because the indicator solutions are not isohydric (see Kolthoff and Kameda, J. A. C. S., *53*, 825, 1931).

Balsamum Peruvianum—The official directions for determining acid value result in a titration figure of but 2 to 3 cc. Use of tenth-normal alkali or a larger sample is indicated.

Balsamum Tolutanum—Size of sample specified for the determination of acid value should be increased to provide for greater precision.

Caffeina cum Sodii Benzoate—Same recommendation as for benzoic acid with respect to the assay for sodium benzoate.

Chlorobutanol—An assay is recommended. See Jour. Assoc. Off. Agr. Chem., *22*, 95, 1939.

Codeinae Phosphas—Titration of the excess of sulfuric acid added to the assay with N/20 or more dilute alkali is recommended.

Collodium—An upper limit of 5.5 per cent. of pyroxylin is recommended.

Cyclopropanum—Use of halogen-free air in the test for halogens should be specified.

Emulsum Olei Morrhuae—Official specification for alcohol content in the case of a product intended to be kept for a period of time is requested.

Emulsum Petrolati Liquidi—Official specification of the limits of alcohol content is requested.

Glycerinum—A refractive index test, with limits of 1.4696 to 1.4726 at 20 degrees C., is recommended. The B. P. Commission's General Chemistry Committee also recommends a test for the absence of certain reducing substances; this test appears to be a desirable addition to the U. S. P. monograph.

Iodoformum—An assay is recommended. See report of the British Chemistry Committee.

Liquor Magnesii Citratis—The 26 cc. minimum titration figure for total citric acid is but 3.4 per cent. below the 26.9 cc. which would be required if 33 gms. of citric acid were used. This tolerance is not consistent with tolerances established for products of similar complexity.

Liquor Sodii Chloridi Physiologicus—An assay for chloride content is recommended.

Magnesii Sulfas—The use of a Gooch crucible in the assay should be directed. Filter paper cannot be used.

Methylrosanilinae Chloridum—Use of Crystal Violet as a synonym for the official substance is erroneous, for the former is hexamethylpararosaniline chloride and the latter is a mixture.

Oleum Cinnamomi—An assay utilizing hydroxylamine hydrochloride is considered superior to the present assay.

Oleum Menthae Viridis—Same comment as for oil of cinnamon.

Oleum Olivae—A test for teaseed oil adulterant is recommended.

Paraffinum—Following a careful study of the test for carbonizable substances in paraffin it is concluded that the term "pale amber" is subject to wide variation in interpretation, that emulsions form between acid and paraffin, and that while several modifications of the test were made, none permitted a satisfactory interpretation to be made.

Potassii Bromidum—See the recommendation for ammonium bromide.

Potassii Chloras—Addition of phosphoric acid before titration with potassium permanganate renders the end point much more distinct.

Quininae Sulfas—An assay is considered advisable.

Sapo Mollis—The officially prescribed determination of acid value results in a titration figure of over 300 cc. Use of a one-gram sample is recommended.

Sodii Biphosphas—Thymolphthalein is a better indicator than phenolphthalein in the assay. See the comment under phosphoric acid.

Sodii Bromidi—See the recommendation under Ammonium Bromide.

Sodii Chloridum—The test for neutrality is not satisfactory because the indicator solutions are not isohydric. See the comment under distilled water.

Spiritus Chloroformi—The assay calls for the use of potassium thiocyanate which is not described in the U. S. P.

Styrax—The quantity of sample used in the determination of acid value should be increased, or the strength of alkali decreased, to provide for greater precision.

Sulfanilamidum—The present assay permits the presence of 3 to 4 per cent. of acetylsulfanilamide without having the result fall below 99 per cent.

Syrupus—Limits of optical activity are suggested as being of value in standardizing this important substance.

Tabellae Glycerylis Trinitratis—Dissatisfaction with the present method of extracting with ether is very general. One laboratory recommends shaking out nitroglycerin with ether after disintegrating the tablets with water. Another recommends separation of nitroglycerin by the distillation method described in the Jour. Assoc. Off. Agr. Chem., *20*, 569, 1937.

Thyroideum—The ceric sulfate assay of Hilty and Wilson, published in the Jour. Ind. Eng. Chem., *11*, 637, 1939, is advocated by several chemists who have tried the method, as being superior to the U. S. P. assay.

Tragacantha—Standardization of this substance is recommended.

Unguentum Hydrargyri Oxidi Flavi—Because of chemical combination of mercuric oxide with components of the base, the apparent content of the former, as disclosed by the official assay method, diminishes as the preparation ages. A non-reactive base should be selected, or an assay for total mercury adopted.

Vanillinum—The color tests under tests for identity has been found to be unsatisfactory. It is also recommended that an assay utilizing reaction with 2:4-dinitrophenylhydrazine be adopted.

General Tests, Processes and Apparatus

Alcohol Determination—Specification of a definite temperature at which the volume of the preparation to be tested is to be measured and the specific gravity determined, is recommended.

Ash Determination—It is suggested that a maximum and minimum ignition temperature be given for each official substance on which this determination is to be made. The apparent ash content varies appreciably with temperature at which the ignition is made.

Assay for Alkali Salts of Organic Acids—It is suggested that use of a platinum crucible be specified in the directions. Fusion of alkalis with porcelain is a frequent and troublesome occurrence if crucibles made of this material are used.

Carbonizable Substances Test—This test should be made with a sulfuric acid containing 94.5 to 95.5 per cent. H_2SO_4 as stated on page 441. This requirement is made obscure in individual

monographs by directing use of sulfuric acid. The directions in such monographs should specify use of this special acid.

Fats and Oils, Determination of Characteristics—In connection with acid value, it is suggested that a uniform method of expressing the value be adopted. At present, some values are given in terms of cc. of tenth-normal sodium hydroxide solution required and others in terms of milligrams of KOH. Because of the relationship between acid value, ester value and saponification value, it would appear that a statement in terms of milligrams of KOH would be advisable in all cases.

In connection with iodine value, the following deficiencies in the official method are pointed out: (1) In the case of oils having an iodine value above 110 (cottonseed, corn) 25 cc. of Hanus' solution does not provide for a 50 per cent. excess of the latter if a 0.3 gm. sample is used, as directed (remedy—use 0.2 gm. sample). (2) In the case of oil of theobroma a similar error is made (remedy—use not over 0.8 gm. sample). (3) The general statement to use 0.8 gm. of solid fat does not allow for a 50 per cent. excess of halogen except in cases where the iodine value is below 41.

Melting Point of Class II Substances—The Wiley method for determining the melting point of fats, etc., is considered to be a better procedure than the capillary tube method in that it permits of greater precision.

Standard Solutions—N/20 and N/50 sodium hydroxide solutions, especially the latter, should be standardized under the conditions of the assay in which each is employed. Standardizing N/50 sodium hydroxide with phenolphthalein as indicator, and then using it in an alkaloidal assay where methyl red is the indicator, is not considered to be good analytical technique.

Viscosity Test—The directions for the test should include important details to be observed, such as control of temperature, technic to be employed, etc. The present test is so worded that a wide variation in results may be obtained. (See A. S. T. M., pages 218-220, 1939, for example.)

Chemical Nomenclature

In general, it is recommended that in all monographs pertaining to substances of known chemical structure, or where the active con-

stituent of the subject of the monograph is of known chemical structure, there be given the generally accepted chemical name for the substance or active constituent. Specific recommendations of chemical names, together with other suggestions falling in this category, are as follows:

Acetophenetidinum—Change paraacetaminophenetol to para-acetaminophenetole.

Acidum Lacticum—Alpha-hydroxypropionic acid.

Acidum Mandelicum—Phenylglycolic acid. Formula in rubric should be $HC_8H_7O_3$ to be consistent with formulas in main volume.

Acidum Nicotinicum—3-pyridinecarboxylic acid. Formula in rubric should be $HC_6H_4O_2N$.

Acidum Salicylicum—Ortho-hydroxybenzoic acid.

Aethylenum—Last part of caution statement is better written ". . . and mixtures of it with oxygen or air *may* explode. . . ."

Aethylis Aminobenzoas—Ethyl para-aminobenzoate.

Aminopyrina—4-dimethylamino-1, 5-dimethyl-2-phenyl-3-pyrazolone.

Antipyrina—1,5-dimethyl-2-phenyl-3-pyrazolone.

Arsphenamina—Change formula to $C_{12}H_{12}O_2N_2As_2.2HCl.2H_2O$ to be in conformance with other hydrochloride formulas.

Barbitalum—5,5-diethylbarbituric acid.

Barbitalum Solubile—"Soluble barbital contains barbital sodium equivalent to not less than . . . etc." is suggested as being a more exact description of the rubric.

Caffeina—1,3,7-trimethylxanthine.

Cyclopropanum—Formula in purity rubric should read $\overline{CH_2.CH_2.CH_2}$. Caution to be modified as suggested for ethylene.

Ephedrina—Laevo-alpha-(1-methylaminoethyl)-benzyl alcohol.

Ephedrinae Hydrochloridum—Change "contains" to "yields" in rubric.

Ephedrinae Sulfas—See preceding recommendation.

Epinephrina — Laevo-3,4-dihydroxy-alpha-(methylaminomethyl)-benzyl alcohol.

Eugenol—4-allyl-2-methoxyphenol.

Glycerinum—Propantriol.

Guaiacol—A liquid consisting principally of orthomethoxyphenol.

Histaminae Phosphas—Change β-iminazolylethylamine to 4-imidazoleëthylamine.

Iodophthaleinum Solubile—Same style of definition recommended as proposed for soluble barbital.

Menthol—Hexahydrothymol or 3-paramenthanol.

Oleatum Hydrargyri—Same style of definition recommended as proposed for soluble barbital.

Pentobarbitalum Solubile—Same style of definition recommended as proposed for soluble barbital, with the further suggestion that the chemical name 5-ethyl-5(1-methylbutyl)-barbituric acid be used for pentobarbital.

Phenobarbitalum—5-ethyl-5-phenylbarbituric acid.

Phenobarbitalum Solubile—Same style of definition recommended as proposed for soluble barbital.

Resorcinol—Meta-dihydroxybenzene.

Sulfanilamidum—Para-aminobenzenesulfonamide.

Theophyllina—1,3-dimethylxanthine.

Thiaminae Hydrochloridum—Change formula to $C_{12}H_{17}ON_4SCl.HCl$ to be in conformance with other hydrochloride formulas.

Thymol—Para-isopropylmetacresol.

Trinitrophenol—2,4,6-trinitrophenol.

Vanillinum—3-methoxy-4-hydroxy-benzaldehyde.

COMMITTEE: Maurice L. Augenblick, Russell Cain, Joseph Ciminera, Lee G. Cordier, Ralph R. Foran, Walter C. Fulmer, Edward J. Hughes, Lewis J. Kleckner, Donald P. LeGalley, E. Emerson Leuallen, Robert L. McNeil, Jr., Ibert Mellan, George W. Perkins, Nathan Rubin, Freeman P. Stroup, Julius W. Sturmer

Arthur Osol, *Chairman*

April 25, 1940
Philadelphia, Pa.

REPORT OF THE SUB-COMMITTEE ON PHARMACY OF THE U. S. P. COMMITTEE OF THE COLLEGE

The following report is based on certain recommendations submitted by various members of the sub-committee. The proposals made are not to be interpreted as representing the unanimous opinion of the sub-committee, but only as suggestions for consideration by the appropriate group during the week of revision.

The items are arranged for convenience according to the Latin title of the drug or preparation to which they relate. Following these a few unclassified suggestions are appended.

Acidum Lacticum—The use of this substance in the preparation of modified milk formulas for infant feeding would seem to warrant a statement as to the average dose for such cases.

Emulsum Asafoetidae—This preparation rapidly spoils due to the growth of mircoorganisms and, furthermore, the therapeutic effect is lost. A statement should be included to the effect that it should be freshly prepared when needed. Since in some cases it is administered orally the use of syrup replacing all or part of the water might be made optional.

Emulsum Olei Morrhuae—The statement "The methyl salicylate may be replaced with no more than 1 per cent. of any other flavoring substance . . ." is misleading. For instance, Emulsum Petrolati Liquidi has only 0.004 per cent. of vanillin as flavoring agent, other unofficial emulsions have as much as 10 per cent. tincture of sweet orange peel as flavoring agent. The statement should be deleted, since in each case the pharmacist should use his own judgment in determining the amount of flavoring substance to be used.

Emulsum Petrolati Liquidi—The statement "In preparing emulsion of . . . other methods of emulsification may be used and the quantity of acacia may be reduced or replaced by agar, gelatin, tragacanth, or mixture of any of these providing the resulting emulsion is similar in viscosity and appearance to that made by the above formula," should have the part beginning with provided . . . deleted. Since the purpose of emulsification is solely one of increasing the palatability, a variation in viscosity is of no importance. The product made by the official formula, although suited to small scale preparation, is too thick for general

acceptance. The viscosity should be permitted to vary provided the oil content is not altered.

Ephedrina—The official ephedrine should be required to be anhydrous in order that it may be suitable for oil solutions.

Fluidextractum Ergotae

Fluidextractum Ipecacuanhae

Some improvement in these two galenicals should be attempted since they are not thought to be fully satisfactory.

Liquor Epinephrinae Hydrochloride—The statement concerning the preservation of such solutions intended for parenteral use should be made more conspicuous in the monograph, possibly in the same manner as the Storage Requirements by the use of a separate paragraph labelled **Preservation** in bold face type.

Liquor Cresolis Saponatus—Recent work has shown that this preparation may be more easily prepared by using soap and cresol directly and dissolving in water. The saponification of linseed oil, now a part of the official method, might be replaced by the alternative of using a suitable soap directly. Some study should be directed as to the possible use of a perfume oil in this product in order to, at least in part, mask the cresol odor.

Liquor Magnesii Citratis—The note permitting the use of CO_2 under pressure to carbonate the solution is ambiguous. It is strongly urged that this be changed and that the practice of carbonating the preparation with CO_2 *without the addition of alkali bicarbonate* be expressly interdicted. The addition of bicarbonate results in the formation of about 2.7 gm. or 41 gr. of potassium citrate, almost 3 U. S. P. doses. The practice of certain manufacturers of leaving this out is for the purpose of using less citric acid which, due to the lenient U. S. P. assay, is possible. The therapeutics of solution of magnesium citrate have been established on its formula which contains alkali citrate and in many cases, e. g., as an abortive measure for a cold, the diaphoretic and diuretic action of the alkali citrate is important.

It is also suggested that the oil of lemon either be deleted or the amount used reduced.

Liquor Sodii Chloridi Physiologicus—Since 0.9 per cent. NaCl is required to give a freezing point depression equal to that pro-

duced by blood serum, the question is raised whether this should not be the NaCl concentration of this solution rather than 0.85 per cent. Such is the case in the B. P., also D. A. B.

Mistura Opii et Glycyrrhizae Composita—Since the ethyl nitrite used in this preparation is known to rapidly deteriorate its inclusion in the product is of doubtful value unless freshly prepared.

Oleum Morrhuae—It has been shown that both rancidity and loss of vitamin A is catalyzed by the oil which adheres to the neck of the bottle which is oxidized and then in part washed back on future pouring. A statement in the monograph directing that the neck of the container be wiped after pouring would greatly prolong the stability of this important drug.

Pulvis Cretae Compositus—The possibility of using powdered tragacanth in place of acacia as the suspending agent has been suggested.

Pulvis Senna Composita—The incorporation of a small amount of powdered tragacanth might assist in the suspension of the powder when it was mixed with warm water before taking.

Spiritus Camphorae—The extensive use of this spirit on the lips for "fever blisters" would seem to warrant the inclusion of a small amount of glycerin in the formula. This addition gives a solution which, when the alcohol evaporates, leaves a smooth film on the surface.

Spiritus Menthae Piperitae
Spiritus Menthae Viridis

The alternative use of chlorophyll color or suitable certified dye is suggested in place of the dried leaves.

Syrupi—In many official syrups the use of simple syrup in the formula might replace the use of sucrose and water.

Tinctura Nucis Vomicae—This galenical should be studied with a view of improving its quality and uniformity.

Tragacantha—It is recommended that a viscosity requirement be included, together with a suitable test for the same. The viscosity of tragacanth varies as much as 300 per cent.

Unguenta—The addition of water to many of the official ointments would improve both their stability against heat or cold as well

as increase their germicidal effectiveness. By forming a water-in-oil emulsion the product is not as liable to liquefy at high temperatures or to lose its plasticity at low temperatures.

A test for fineness of the product, such as rubbing between glass slides, might also be included in the monograph.

The possibility of the inclusion of some of the newer vanishing cream type ointment bases should be considered if agreeable to the Committee on Scope.

Unguentum Hydrargyri Ammoniati
Unguentum Hydrargyri Oxidi Flavi

In each of these preparations it is suggested that the mercury compound be freshly precipitated before incorporating into the base following the procedure outlined in the German and Swiss Pharmacopoeias.

Unguentum Iodi—If used as an antiseptic, this ointment is far too strong. It is definitely counter-irritant and since iodine is probably the No. 1 antiseptic of the whole list, this strength should be reduced to 0.5-1.0 per cent. or another ointment of such strength adopted.

The following general suggestions are made:

I. Some consideration should be given under alkaloidal salts to the best method of sterilizing each one in aqueous solution without extensive deterioration.

II. The recognition of concentrates for the purpose of making tinctures or syrups should receive some attention.

III. There are several drugs in the Pharmacopœia that seem like proprietaries since they are available from only one source, e. g., Chiniofon Powder, Calcium Iodobehenate, etc.

IV. Although not strictly a function of the sub-committee on pharmacy, certain members of our group deplore the trend of the Pharmacopœia to minimize the importance of certain preparations. There are many classes of preparations that should be in this book since their inclusion would both assist the physician to prescribe and use official preparations as well as create more interest in the Pharmacopœia by both physician and pharmacist. Should the book become simply a list of standards, its utility and service to medicine and pharmacy would be greatly impaired.

This is directly in accord with the recent action of the Pharmaceutical Society of Great Britain which has unanimously recommended such a program for the next revision of the British Pharmacopœia.

We would urge the adoption of preparations to provide a convenient mode of administration for substances now recognized only in pure form. As an example, we feel that both tablets and an elixir of thiamin hydrochloride should be adopted. The physician should have available official preparations offering such substances in divided doses so that he may prescribe them without the necessity of remembering the dose and attempting to formulate a prescription for them.

Respectfully submitted,

IVOR GRIFFITH, *Chairman,*
L. F. TICE, *Secretary.*

REPORT OF P. C. P. & S. SUB-COMMITTEE ON PARENTERAL SOLUTIONS

Aqua Destillata Sterilisata

This preparation is very generally administered in large quantities parenterally, and it is therefore recommended that a pyrogen-free distilled water be used and a test for pyrogen in the final preparation be included in the proper position.

The present monograph calls for water which is neutral to litmus paper. The official distilled water carries more exacting specifications for pH than is obtained by the use of litmus paper. Surely sterilized distilled water should be the equivalent of distilled water in this respect, and we suggest therefore that this portion of the monograph read as follows:

> "Distilled water, freshly prepared, a sufficient quantity. Place the freshly prepared distilled water in sterilized containers, etc."

It is important that solutions for parenteral use be free from fibers and filaments, and we therefore question the use of cotton plugs in the preparation of sterile distilled water, since such plugs are almost certain to cause filament contamination.

The storage clause states that if the water is "stored in an hermetically sealed container it should conform to the tests for sterility of liquids, page 469." The very name "Sterile Distilled Water" would indicate that the preparation should conform to the tests for sterility under any conditions.

Liquor Epinephrinae Hydrochloridi

Under storage, one is directed to "preserve Solution of Epinephrine Hydrochloride in small, well-filled, amber-colored bottles or in ampuls." Should ampuls be defined? Is a multiple dose container an ampul? Ampuls indicate parenteral administration, which is also mentioned under the dose statement. Under such conditions the preparation should conform to the tests for sterility of liquids, page 469. A statement to this effect should be added.

Liquor Hepatis Purificatus

A statement that this solution conforms to the tests for the sterility of liquids, page 469, should be included in this monograph.

Liquor Histaminae Phosphatis

Being a solution primarily for parenteral use, the distilled water which is used should be pyrogen-free and the solution should conform to the tests for sterility of liquids, page 469.

Liquor Parathyroidei

A statement that the solution conforms to the tests for sterility of liquids, page 469, should be added.

Liquor Sodii Chloridi Physiologicus

A true isotonic solution of sodium chloride is one which contains 9.1 Gm. of Sodium Chloride per 1000 Gm. of water. The slightly rounded figure of 9 Gm. is used by the British, Swiss, Danish, Italian and Estonian Pharmacopœias and probably others. It is recommended that the U. S. P. adopt 9 Gm. of sodium chloride as the basis for this solution.

Where this solution is used parenterally it should be prepared from pyrogen-free distilled water, as pyrogens become very objectionable where large quantities of solution are administered as is often the case with this preparation.

We recommend that the advisability of an assay for this solution and the question of the use of sodium chloride of possibly higher standards also be considered.

Sterilization Chapter and Tests for Sterility of Liquids

These chapters should be carefully checked throughout.

Sterilization by steam under pressure is usually conducted at fifteen pounds (121 degrees C.). References to steam pressure should be made uniform and the temperature always included in such a statement.

In the preparation of ampuls and bottles for solutions it is thought that 0.1 per cent. of hydrochloric acid is sufficient for normal washing purposes, although stronger solutions might be desirable in extreme cases.

General Notices—Preservation of Solutions for Parenteral Use

The present paragraph reads as follows: "For the preservation of solutions of organic substances intended for parenteral administration, there may be added to the solution, unless otherwise directed in the monographs, not more than 0.5 per cent. of chlorobutanol, cresol, phenol, sulfurous acid, sodium bisulfite or other suitable preservative. Not more than 0.85 per cent. of sodium chloride may be present, and the air in the container may be replaced by carbon dioxide or nitrogen. The presence and amount of the preservative shall be plainly declared upon the label of the container in which it is sold or dispensed."

We suggest that the word "organic" be deleted from the second line of the paragraph in order to make the preservation clause apply to all types of solutions.

Sulfurous acid and sodium bisulfite are preservatives of an entirely different nature from chlorobutanol, cresol, etc., and should be considered separately. Often we find a preservative of the first type used in conjunction with one of the second. Limiting "other suitable preservatives" to 0.5 per cent. concentration does not seem justifiable and we would suggest that this portion of the text be changed to read "and other suitable preservatives in adequate amount may be used in place of the above." It would appear that the 0.5 per cent. limitation was based upon the chlorobutanol group. Possibly a limitation should also be included for the sulfite type.

Reference to sodium chloride would seem to be out of place in this paragraph on preservatives. We question the need for such a statement, but if it is necessary it should be placed elsewhere.

The last sentence should be made to read "The presence of carbon dioxide or of nitrogen, and the presence and amount of other

preservatives shall be plainly declared upon the label, etc." Considering carbon dioxide and nitrogen as forms of preservatives, it would be rather difficult to "state the amount" which is present.

General Chapter

In view of the above varied comments it might be desirable for the U. S. P. to consider a general chapter which would include these numerous aspects of preparations for parenteral use under a common heading. This would cover sterilization, sterility tests, preservation, containers, basic physical characteristics of solutions, etc. We recommend that this be considered for U. S. P. XII.

ADLEY B. NICHOLS, *Chairman,*
R. L. MCNEIL, JR., *Secretary.*

REPORT OF THE SUB-COMMITTEE ON BIO-ASSAYS

It is urgent both from the viewpoint of the manufacturing pharmacist and the physician and, of course, ultimately the patient in each instance, that any revision in bio-assay methods be most carefully approached. The present co-operative attitude as expressed in the pharmacopœial studies now under way should bring new methods or modifications of old methods into official acceptance that will not be subject to the many criticisms now leveled at them. A more fixed opinion as to their value must be established.

Just as criticism now is justly made of present methods, we shall likewise see this criticism extended if the Pharmacopœia endeavors to go beyond its purpose or scope. The Pharmacopœia is intended to provide a means for determining the strength, purity and identity of items official therein. Recent bio-assay text has stepped beyond this purpose or intent, and we find that methods are suggested for which no product exists in the U. S. P. In fact, these methods are required. Required in the face of conditions which mean that even though required they may not be applicable. Specifically we refer to the Thiamine Hydrochloride or Vitamin B_1 assay in the Second Supplement of the U. S. P. XI, which reads:

> "The assay of products for thiamine HCl or Vitamin B_1 potency shall be by comparison with the U. S. P. Reference Standard Thiamine HCl by assay procedure conforming in all respects to the following specifications:"

This statement is obligatory and applies to all products whether dog food, infant food, pills, tablets or any specialty, and yet there is not a single item official in the U. S. P. which requires such an assay. An attempt has been made to include all items and products, even though the assay may not be adaptable. It is a policy fraught with danger, both to the Pharmacopœia and to those who now make use of its standards.

It would be futile to make numerous and varied recommendations in regard to bio-assays in the face of the intensive studies under way. However, our desire is to suggest certain modifications which may be of value.

Aconite and its preparations

It is generally conceded that the present method of aconite evaluation does not represent its useful value. However, no other method is available which can be applied, and which has behind it the necessary experience.

It is recommended, therefore, that certain changes be made in the assay directions in order to more clearly state their intent and to improve the accuracy of the assay. The cost of properly performing an aconite assay is of such magnitude that manufacturers cannot hope to have a suitable margin of profit returned on aconite preparations. Nevertheless, solely on the basis of a need for increased accuracy, the changes we are recommending will materially increase this cost.

In general we are suggesting a greater permissible range in pig weight. This will make it somewhat easier to obtain the necessary increased number of animals; that not less than sixty pigs must be used in each assay including those employed on both standard and preparation. This will make for greater accuracy. Prohibit the use of previously employed animals. Permissible use of aconitine for six months and then its discard. The present directions require a comparison of six months old standard with a freshly prepared aconitine solution. The cost of such comparison is out of proportion to the probable benefit; it is far more economical and also more advisable to discard; such a comparison costs between $80 and $150, when new standard could be prepared for less than $5.00. Definite dilutions, directions for both standard and sample to assure uniform absorption.

It is recommended that we specifically suggest:

1. Not less than three different dose levels be required, each level having not less than ten guinea pigs thereon, for both the standard and the unknown. The levels so used shall show quantitative differences in response.
2. That to be a valid assay, the response in all of these levels shall be not less than 10 per cent., nor greater than 90 per cent.
3. One level may be selected for comparison, which level shall give a response for both standard and unknown of between 30 and 70 per cent., but that no two levels shall be compared which differ by a greater difference than one pig in every ten used.
4. Pigs shall be deprived of food but not of water for a period of twenty-four hours before their use.
5. Pigs varying between 250 and 400 grams in weight may be used, provided all pigs employed in a final assay shall not vary greater than 50 grams from one another.
6. All pigs employed in an assay shall be healthy animals which have not previously been used for testing aconite or any other preparation.
7. Pigs previously employed for testing aconite may be used for determining an approximate level preliminary to running a final assay.
8. Standard aconitine solution may be kept for a period of six months in sealed hard-glass ampuls at a temperature not above 10 degrees C.
9. Suitable dilutions of standard and of the preparation shall be used so that 0.002 cc. of this dilution may be given for each gram body weight of pig.
10. That study be given to the possibility of using statistical methods of evaluation.

Digitalis

The present digitalis assay studies will no doubt change the entire character of the digitalis assay which will appear in the forthcoming U. S. P. XII. These studies have been carefully planned with the thought that they will assure not only more accurate assays

but also be applicable to products other than Tincture of Digitalis or Digitalis Leaf.

As there is a desirable tendency towards the increased use of powdered digitalis in some form such as the tablet, pill or capsule, these should be made official in the forthcoming revision, together with a method of assay. In such products factors will present themselves which usually will not be manifest in the examination of tincture or dried leaf. For instance, the method of extracting the drug activity will be of prime importance. Consideration must be given to the probable diluents in the tablet, pill or capsule, and the effect they may have upon the absorption of the assay dose of drug extractive. It may even be advisable for the sake of uniformity to specify the diluents that may be permissible or the excipients that can be employed as binders in preparing capsules, tablets or pills. In addition the capsule, pill or tablet weight possibly should be controlled, within a definite maximum ratio of weight to drug strength. Such control will avoid the use of excessive quantities of diluent which may later appear in the drug extractive and adversely affect absorption, thus vitiating the test.

Experience has shown that doses of drugs given in the upper portion of the ventral lymph sac are much more rapidly absorbed than those given in the abdominal section of the lymph sac. This effect varies considerably, but the drug may be said to be roughly twice as toxic in the upper section than in the lower, at least by the one hour frog method. This variation in dose effect may no doubt be the cause for some criticism of the one hour method, for in some cases more uniform response is obtained by the upper route.

Experience recently indicates that when a high level dosage of drug is required in the one hour method and it is given by the lower route, much more irregularity of response is observed at different dose levels than when given by the upper route.

We recommend that before adopting any change in the assay, which will mean a material revision, that a study be initiated to establish the applicability of such assay to tablets, pills and capsules. It is further recommended that the requirement now appearing in the present text in regard to frog sensitivity, namely that not more than 0.003 cc. of the standard tincture per gram weight of frog be required to produce systole, should be deleted if the one hour method again becomes official and no similar statement be used if the eighteen hour method is introduced.

Pituitary

Clarification of the directions for the preparation of the pituitary standard used in this assay is desirable, and the following is suggested:

> "Heat this mixture to the incipient boiling point for one minute and filter while hot through a small filter paper in a covered funnel."

It is further suggested that the maximal weight of the guinea pigs used in this assay should not be restricted to the 350 grams, as at present, but that any guinea pig be satisfactory for use providing it is a virgin pig and not in heat.

Particular attention should be given to the possibility of impurities being present in the chemicals used to prepare Locke-Ringer Solution which may affect the assay. It will likely be desirable to set up new standards for both the chloride and the calcium chloride used in the Locke-Ringer Solution, and possibly for the other chemicals as well. Samples of calcium chloride have been observed which will contribute more magnesium to the Locke-Ringer Solution than is directed to be used in the assay.

Glass-distilled water is unnecessary in making Locke-Ringer Solution, and an alternative should be provided such as recently-distilled water of low conductivity.

Further, it is suggested that the Pharmacopœia drop all reference to any direction for making a standard pituitary powder and restrict standard pituitary powder to that which is distributed by the Pharmacopœial Committee.

Epinephrine Solution

It is recommended that the requirement for dilution to 1:100,000 be deleted, as this is too great for optimum results. The requirement should be that a satisfactory dilution be employed to give a dose response of 30-60 millimeters when not more than 1 cc. or less than 0.5 cc. of the dilution is administered.

It is further recommended that the suggested limit for return of blood pressure to normal before subsequent injections should be removed, but a statement inserted that normality shall have re-established itself.

Test animals used in this assay should be acclimated to the surroundings by being held on a good and sufficient diet for one week before being used for the assay.

It is further recommended that some revision in the text should be made to require proof of submaximal response in the most sensitive range of the assay, i. e., equality of response at two or more dose levels.

Insulin

It appears that the method of assay as used by the Insulin Committee, Laboratory of the University of Toronto, as published in the Quarterly Bulletin of the Health Organizations of the League of Nations, Volume on Biological Standardization II, Special Number, November, 1936, is satisfactory.

It is suggested it be required that in evaluation of insulin potency, the dose must fall in the straight line portion of the dose response curve. It is further suggested that as the dose of insulin required in this assay varies with the climatic variation, it is advisable that the conditions under which the animals are stored and the assay performed, be carefully specified. Insulin assay is an expensive procedure and should be undertaken only under the most optimum conditions.

Ergot and its preparations

The assay for ergot given in the Pharmacopœia requires an estimation of the darkening of the cock's comb within one hour to one and one-half hours following the injection into the breast muscles. Maximal darkening of the comb very often occurred in forty-five minutes, rather than one hour. Directions should be modified to allow for the reading at the period of maximal darkening of the comb.

In cold weather, greater response is obtained than in warm weather to the same dose of ergot. Cocks should therefore be restandardized if there has been any definite change in climatic conditions unless kept in quarters of fairly uniform temperature.

It is further recommended that attention should be given to a more satisfactory method for the evaluation of ergot and that chemical determinations or cock's blood pressure methods be carefully considered.

We also suggest that the Pharmacopœia adopt a uniform method for recording the results obtained when bio-assays are performed. This might be accomplished by including in the Pharmacopœial text sample forms to be followed by bio-assayists. On the other hand, inasmuch as the Pharmacopœia now by necessity distributes bio-

assay standards, they might also make available such forms to bio-assayists. It is not our desire to prevent the recording by those engaged in this work such additional data as they may deem advisable. However, the use of standard recording forms would be distinctly advantageous. It would insure uniform recording of observed conditions and would thereby be likely to increase the accuracy of interpretation between different bio-assayists. Such data uniformly recorded would lend itself to other uses, especially future study of the assay procedure when such might appear to be advantageous.

It is probably true that each major laboratory engaged in this work follows a method of recording which they may feel is the most suitable to their needs. Yet it is obvious that if certain uniform facts were available an increased value would attach to routine bio-assays. Special studies on bio-assay when undertaken may be said to closely approach handling under extraordinary care and not duplicate practical conditions. Any method which will enable a study to be undertaken upon routine bio-assays should therefore be of practical value. The Chairman of this Sub-Committee has at hand a volume designed and about to be put in active use by Sharpe and Dohme to record the results of digitalis assays. Based upon an adoption of the outline of the present Pharmacopœial digitalis study, it is illustrative of what may be a suitable design for a Pharmacopœial form. The accompanying photostat can be more easily observed.*

Respectfully submitted,

J. W. E. HARRISSON, *Chairman,*
Sub-Committee on Bio-Assays.

*Photostat not supplied with the bound report.